REMARKS

STATUS OF THE CLAIMS

Claims 1-72 were pending. Claims 7, 9, 14-16, 34-42, 71 and 72 have been withdrawn from consideration. Independent claims 1 and 43 have been amended herein to make explicit what was previously implicit. In particular, it is now made explicit that the fusion molecules comprising the chromatin remodeling polypeptide do not themselves regulate transcription, as described throughout the specification, for example on page 5, lines 9-12. Thus, claims 1-72 are pending as shown above, and claims 1-6, 8, 10-13, 17-33 and 43-70 are under consideration.

Applicants acknowledge the withdrawal of previous rejections under 35 U.S.C. §§ 112 first paragraph, 102(e) and 103(a).

INTERVIEW SUMMARY

Applicants' representative Sean Brennan held a personal interview on February 19, 2004 with Examiners Akhavan and Leffert. At the interview, previous rejections under 35 U.S.C § 112, first and second paragraphs, and 35 U.S.C § 103 were discussed and agreement was reached that those rejections would be withdrawn. The previous obviousness-type double patenting rejection and potential new rejections under 35 U.S.C. Section 112, first paragraph, were discussed, and agreement was not reached. Applicants thank Examiners Akhavan and Leffert for their time at the interview and for their thoughtful attention to the application.

OBVIOUSNESS-TYPE DOUBLE PATENTING

The provisional rejection of claims 1-6, 8, 10-13, 17-33 and 43-70 under the judicially created doctrine of obviousness-type double patenting, has been maintained. The Office Action alleges that the aforementioned claims of the present application are directed to the same invention as that of claims 1-15 and 17-20 of co-pending application no. 09/942,087. (Office Action, pages 3-4). In support of the rejection, the Examiner states, in part:

> While the applicant makes a rational argument, it does not answer in the negative the salient question, do the reference claims anticipate the instant claims. Indeed the answer is yes because modifying chromatin structure is a prerequisite for modulation of gene expression. In other words, while chromatin accessibility may not be sufficient for regulation of transcription, it certainly is necessary for such regulation. (Office Action, pages 3-4).

Applicants respectfully traverse this provisional rejection and the supporting remarks, because the Office's statements in support of this rejection are incorrect.

First, modification of chromatin structure is not a necessary prerequisite for regulation of transcription. As described throughout the specification as filed, DNA-binding domains are known that bind to inaccessible regions and modulate transcription. *See, e.g.,* the paragraph beginning on page 23, line 7 and on page 54, lines 20-26. Furthermore, as correctly noted in the first full sentence of page 4 of the Office Action, chromatin may be accessible to regulatory molecules without prior modification for any number of reasons. Therefore, it is not always the case that a transcriptional regulatory molecule always alters chromatin structure, nor is it always the case that binding of a transcriptional regulatory molecule to DNA requires chromatin remodeling. The corollary is also true -- a molecule that alters chromatin structure does not always regulate transcription.

Indeed, one need look no farther than the references cited by the Office to find ample evidence that the Office's statement that ". . . while chromatin accessibility may not be sufficient for regulation of transcription, it is certainly necessary for such regulation" (office action, page 4, lines 1-2) is incorrect. For example, Felsenfeld, *et al.* (reference U) state: "In some cases, the packaging of particular genes in chromatin is required for their expression." (page 449, second column, 6th full paragraph, emphasis added). Felsenfeld also states: ". . . some DNA sequences are accessible either as an outward-facing segment on the nucleosome surface, or in the linkers between nucleosomes . . ." (Felsenfeld *et al.*, page 449, second column, paragraph bridging pages 449-450); in these latter cases, chromatin accessibility is not even necessary (let alone sufficient) for transcriptional regulation.

Reference claims 1 and 13 provide no indication that chromatin structure is altered by a DNMT, nor does the specification of the 09/942,087 application support such alteration. For example, action of a DNMT as claimed in the reference claim could alter transcription simply by altering the sequence of a binding site such that it is no longer bound by a regulatory protein (*e.g.* a protein that is unable to bind methylated DNA) without any alteration of chromatin structure.

In summary, the claims of 09/942,087 are directed to methods for modulation of transcription. In contrast, when a fusion of a chromatin remodeling polypeptide and DNA-binding protein that alters chromatin structure is used in the presently claimed methods, this

fusion never itself regulates transcription. This is entirely different from the methods and proteins of 09/942,087, which relate to proteins and methods that necessarily regulate transcription. Thus, the presently claimed methods (and molecules used in these methods) are not anticipated by the claims of 09/942,087.[1]

Therefore, for all of the reasons of record and those reiterated herein, Applicants believe that the present double patenting rejection is improper because it is based upon incorrect assumptions regarding the relationship between chromatin remodeling and transcriptional regulation.[2] Accordingly, this rejection should be withdrawn.

35 U.S.C. § 112, ENABLEMENT

Claims 1-6, 8, 10-13, 17-33 and 43-70 were rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (Office Action, pages 5-9). In particular, the Examiner maintains that the specification does not enable *in vivo* methods. In support of this rejection, the Examiner also cites several references (Anderson, Armstrong, Morales, Wang, Urnov, Check, etc.) as allegedly demonstrating that the claimed methods are somehow unpredictable. (Office Action, page 4).

Because the specification fully enables the claims throughout their scope, Applicants traverse the rejection and supporting remarks.

SCOPE AND NATURE OF THE CLAIMS

As the Examiner correctly notes, an enablement inquiry must begin with interpretation of the scope of the claims. *See, In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988). In the pending case, however, the Examiner errs in interpreting the pending claims to be drawn to methods of gene therapy:

---

[1] Applicants note that the Office Action states that the claimed methods and fusion proteins facilitate transcriptional activation (Office Action, page 3). This, too, is incorrect, as the claimed methods and compositions can also facilitate transcriptional repression, as well as replication, recombination, integration and a number of processes which depend upon access to cellular chromatin. *See*, for example, the specification at page 13, lines 10-16. This is also admitted in the Office Action at page 4, third full paragraph, last sentence.

[2] See also the specification at page 55, lines 7-17 for disclosure of the distinction between modification of chromatin structure and regulation of transcription.

> Furthermore, to the extent that the invention is drawn to *in vivo* use, the invention is necessarily directed to gene therapy (*e.g.*, altering DNA expression patterns), because whether the fusion protein is administered though a gene altering or non-gene altering vector (*e.g.*, viral or liposomes), the method is directed to accessing chromatin in the nucleus of the cell and results in altered gene expression, for example. The only disclosed utility for such *in vivo* embodiments is for therapeutic effect. (Office Action, page 6).

As noted above, there is absolutely no requirement in examined claims 1-6, 8, 10-13 and 17-33 that gene expression be altered. In fact, these claims specifically exclude methods in which a fusion protein comprising a chromatin remodeling complex and a DNA binding domain directly modulates gene expression. Moreover, there is absolutely no requirement in any of the claims, including claims 43-70 in which gene expression is modulated, that any diseases or conditions be "treated." All that is required is that chromatin structure be altered (claims 1-6, 8, 10-13 and 17-33) or that gene expression be modulated by a second molecule, other than a fusion protein comprising a chromatin remodeling complex and a DNA binding domain (claims 43-70). Thus, the claims are <u>not</u> drawn to gene therapy methods, but, instead, are directed to methods of altering chromatin structure and/or modulating gene expression.

Seemingly based on the faulty assumption that the claims are somehow necessarily directed to gene therapy methods, the Office further asserts that the only disclosed utility for *in vivo* use is for therapeutic effect. (Office Action, page 6). This is inaccurate. In fact, the specification clearly indicates that altering chromatin structure *in vivo* can serve to facilitate a variety of process. *See,* for example, page 5, lines 9-12 of the specification:

> Disclosed herein are compositions and methods useful for targeted modification of chromatin. These compositions and methods are useful for facilitating processes that depend upon access of cellular DNA sequences to DNA-binding molecules, for example, transcription, replication, recombination, repair and integration.

Thus, not only do the methods **not** require regulation of transcription, there are multiple disclosed *in vivo* utilities for the claimed methods of altering chromatin structure.

Despite the fact that the methods are not required to provide a "therapeutic effect," the claimed methods are limited in ways not noted by the Office. In particular, the claims as amended above clearly require (1) that the fusion proteins comprising the chromatin remodeling complex do not themselves alter gene expression and (2) that chromosomal chromatin is altered.

Simply put, the claims are directed to methods of altering the structure of chromosomal chromatin using proteins that do **not** themselves modulate transcription. When the claims are properly interpreted, Applicants submit that there is no question that the specification as filed fully enables these claims throughout their scope.

UNDUE EXPERIMENTATION IS NOT REQUIREMENT TO PRACTICE THE CLAIMED METHODS

The Office Action also incorrectly asserts that the specification does not provide sufficient guidance regarding gene transfer methods and, accordingly, that undue experimentation would be required to practice these methods *in vivo*. (Office Action, pages 8-9). The Office Action also states:

> For there to be sufficient guidance, the disclosure would have to teach how to deliver the fusion protein *in vivo* to circumvent potential toxicity, an adverse immune response, as well as potential unintended targeting (*e.g.*, activating non-target chromatin containing non-target genes). The disclosure does not provide significant guidance on how to use the invention *in vivo*. (Office Action, page 9).

This is not the proper test of enablement and, moreover, is contradicted by the evidence of record. The proper test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). It has long been settled that determinations of safety (*e.g.*, toxicity and adverse immune reactions) and efficacy are **not** relevant to patentability but, instead, fall under the purview of the FDA. *See, e.g.*, M.P.E.P. § 2107.03 and *In re Krimmel* 130 USPQ 215 (CCPA 1961).

Furthermore, the courts have emphatically rejected the notion that one of ordinary skill in the art must have reasonable assurance of obtaining positive results in all cases. *See, In re Angstadt,* 190 USPQ 214, 219 (CCPA 1976). So long as it is clear that some species render a method operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1 of 35 U.S.C. §112. *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988. Moreover, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof. (*In re Angstadt* at 218; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29, 32, CCPA 1976.)

Thus, in the pending case, Applicants are in no way required to show anything regarding toxicity, absence of adverse immune reactions, or unintended targeting any more than they are

required to show an *in vivo* therapeutic benefit when chromatin structure is altered using the claimed methods. All that is required is that the specification teaches a skilled practitioner how to, without requiring undue experimentation, select a chromatin remodeling polypeptide, how to make a fusion between the chromatin remodeling polypeptide and a DNA-binding domain (or a polynucleotide encoding this fusion) and introduce the fusion protein (or polynucleotide encoding the fusion protein) into a cell to alter the structure of chromosomal chromatin.

The specification more than satisfies this requirement, for example by clearly setting forth a variety of chromatin remodeling proteins and by teaching how to generate fusion proteins comprising these chromatin remodeling proteins. (*See, e.g.,* pages 25 to 34 and the section entitled "Construction and delivery of fusion proteins" starting on page 35 of the specification). In fact, methods of making fusion proteins comprising various chromatin remodeling polypeptides are both disclosed and exemplified. Example 11, for instance, describes how to make polynucleotides encoding fusions proteins comprising ISWI while Example 12 describes construction of a fusion protein comprising SRC-1.

Furthermore, the specification teaches in great detail how to deliver fusion proteins comprising a chromatin-remodeling complex and a DNA binding domain to cells *in vivo* and, in addition, how to assay whether cellular chromatin structure has been modified (and whether or not transcription is altered). Delivery vectors and methods are described, for instances, at pages 44-49 and in the Examples. Assays methods are described, for example, at pages 49-51 and Example 6. The assays described would be routine to the skilled artisan who would also understand their applicability, both *in vitro* and *in vivo*. Thus, the evidence of record plainly establishes that, following the teachings of the specification, one of skill in the art could practice the claimed invention without undue experimentation.

It is axiomatic that working examples are never required to establish enablement. *See, In re Stahilevitz* 212 USPQ 561 (CCPA 1982), in which the CCPA held that broad claims to immunological methods were enabled by the specification as filed despite not disclosing even a single operative embodiment. Even in the chemical arts, an applicant is never required to exemplify multiple embodiments encompassed by the claims. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976). Thus, the presence or absence of examples relating to modification of chromatin structure *in vivo* is not relevant to the instant inquiry. The relevant inquiry remains what the specification teaches one of skill in the art.

With regard to the contention that *in vitro* results would not correlate with *in vivo* results, Applicants direct the Examiner's attention to the large body of work described in the specification, showing that *in vitro* results with fusion proteins comprising a DNA-binding

domain and a transcriptional regulatory domain correlate extremely well with results obtained *in vivo*. *See, e.g.*, page 55, lines 7-17 of the specification and reference cited therein. Thus, based on proven success using fusion proteins comprising DNA-binding proteins and transcriptional regulatory domains, there is every indication that fusion proteins comprising chromatin-remodeling polypeptides and DNA-binding domains would work equally well *in vitro* and *in vivo*.

In brief, the skilled artisan could readily select any polypeptide from any chromatin-remodeling complex; make a fusion protein with a DNA-binding domain and test whether or not chromosomal chromatin structure is altered *in vivo*, again according to the disclosure. If chromatin structure is not altered, the selected fusion protein does not fall within the scope of the claims.

THE CITED REFERENCES DO NOT ESTABLISH UNPREDICTABILITY

A variety of references have been cited, combined with unsupported speculation[3], to allege unpredictability in the state of chromatin remodeling and unpredictability of gene therapy. (Office Action, pages 6-8). In particular, with regard to *in vivo* modification of chromatin structure it is alleged that:

> [I]t would have been highly unpredictable whether a fusion construct once administered to an animal, would first evade the immune system and second, not impart unintended deleterious effects (*e.g.*, toxicity or remodeling non-target sites). For example, as the functionality for the many subunits of the many multi-protein remodeling complexes remains to be elucidated, even if the fusion construct is effectively targeted, the subunit imparting remodeling function may not actually work on the target gene *in vivo*. In addition, the functionality *in vitro* does not necessarily translate into functionality *in vivo*, with respect to the broad class of remodeling complexes claimed. (Office Action, page 7).

Similarly, various references are cited as allegedly establishing unpredictability of gene therapy:

> With respect to unpredictability in gene therapy, the art is still a highly unpredictable area within biology and medicine. For example, vectors used to deliver fusion constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (See, Check, Erika, Feb. 13, 2003, Nature 421:678) (citing occurrence of

[3] For example, ". . . even if the fusion construct is effectively targeted, the subunit imparting remodeling function **may not actually work** on the target gene in vivo." Office action, page 7, emphasis added.

> leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA).... (Office Action, page 8).

As noted above, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). The relevant art is defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc., for which the invention is used. *See, e.g.,* PTO Training Manual on Enablement, page 15.

In regards to chromatin remodeling, the Examiner has cited Urnov et. al. (2002), Morales et al. (2001) Armstrong et al. (1998); Wang et al. (2003) and Anderson et al. (1998) as allegedly establishing the unpredictability of the art as relevant to the claimed invention. As an initial matter, Applicants note that the Armstrong and Anderson references, published in 1998, do not represent the state of the art as of the priority date (August 2000). Moreover, none of these documents relate to methods in which chromatin remodeling polypeptides are used as fusions with DNA binding domains to remodel chromatin structure. Only Urnov discusses anything with regard to DNA binding domains and, post-filing of the specification at issue, simply re-states what is set forth in the specification, namely that chromatin remodeling may facilitate transcriptional regulation. Discussions about chromatin remodeling complexes or chromatin structure do not rise to the level of establishing that the claimed invention is "unpredictable" or that it would require "undue experimentation" to practice the invention. Thus, the cited references are silent as to fusion molecules as claimed. Therefore, these references cannot serve as evidence that it would require undue experimentation to practice the invention as claimed.

Furthermore, as detailed above, potential "unintended deleterious effects" do not in any way establish unpredictability. The Patent Office's role is to examine claims for their compliance with patent statutes, not to determine safety and/or efficacy. Therefore, the question of enablement is what the specification teaches one of skill in the art. Here, for all the reasons noted above, Applicants' specification teaches one of skill in the art how to make and use the methods as claimed.[4]

Finally, the concerns expressed by the Office regarding the unpredictability of gene therapy are not relevant to the pending case. The Examiner's position regarding gene therapy appears to be that because there may be fusion constructs as claimed that do not remodel

[4] Moreover, with respect to the concern about whether the claimed constructs would be able to evade the immune system (Office Action, page 7), Applicants note that a number of mammalian (including human) chromatin remodeling complexes have been disclosed (see, *e.g.*, pages 26-29 of the specification), including brm/BRG, E-RC1, PYR, ATRX, RSF, WCRF and Mi-2.

chromatin but nonetheless somehow integrate into the genome, undue experimentation would be required to practice the claimed methods. This reasoning is entirely improper. Fusion molecules that do not remodel chromatin are not encompassed by the claims. Further, it is well settled that time-consuming or expensive experimentation is **not** undue if it is routine. (See, *e.g.,* PTO Training Manual on Enablement, pages 30-31, citing *United States v. Telectonics Inc.,* USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied* 490 U.S. 1046 (1989) holding the disclosure of a single exemplified embodiment and a method to determine other embodiments was enabling, even in the face of evidence that determining additional embodiments might require 6-12 months of effort and cost over $50,000). For the reasons noted above, it would be routine to make any fusion protein as claimed and assay it for its ability to alter chromatin structure, either *in vitro* or *in vivo*. Thus, the possibility of generating inoperative embodiments allegedly established by the gene therapy references is not germane to the claimed methods.

Thus, when the *Wands* factors are considered, the claims as presently presented are of reasonable scope and are fully enabled by the specification as filed. Accordingly, withdrawal of this sole remaining rejection is respectfully requested.

35 U.S.C. § 103

Claims 1-6, 8, 10, 17-18 stand newly rejected under 103(a) as allegedly obvious over U.S. Patent No. 6,607,882 (hereinafter "Cox") in view of Hsieh et al. (1994) *Mol Cell Bio* 14(8):5487-5495 (hereinafter "Hsieh"). Cox is cited for teaching modulation of gene expression of endogenous cellular genes, which again are alleged to "necessarily comprises remodeling of chromatin structure using recombinant zinc fingers." (Office Action, page 10). In addition, Cox allegedly provides explicit motivation to modify a fusion construct comprising a DNA-binding domain and a transcriptional regulatory protein such that "the transcriptional activator (or repressor) comprising the fusion protein can be substituted with other molecules." (Office Action, page 11). Hsieh is cited for teaching CpG methylation. *Id.* The Office Action continues:

> It logically follows, that it would have been obvious to produce a fusion protein comprising a ZFP and a chromatin remodeling motif, such as a methyltransferase, with the expected benefit of broader application of proteins or effector domains that have the ability to modulate transcription via different mechanisms. Indeed applicant's example illustrating regulation of expression is exactly what Cox teaches: a fusion construct with a methyltransferase (i.e., DNMT) used to repress gene expression. *Id.*

Applicants traverse the rejection and supporting remarks.

As noted above, claims 1-6, 8, 10, 17-18 are directed to methods of altering chromatin structure using a fusion protein comprising a DNA-binding domain and chromatin remodeling complex. Importantly, the fusion protein used in the claimed methods does **not** itself regulate transcription.

There is nothing in Cox or in the combination of Cox and Hsieh that teaches or suggests fusion molecules that do not regulate transcription. Indeed, the entire point of Cox is regulation of endogenous genes. The alleged motivation provided by Cox is not an invitation to design and use molecules that have no transcriptional regulatory functionality, but rather an invitation to design and use molecules that have different transcriptional regulatory functions.

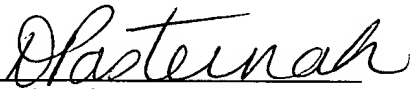
Moreover, cited U.S. Patent No. 6,607,882 was, at the time the present application was filed, owned by Sangamo BioSciences, Inc. (*see* Reel 010847, Frame 0954). In addition, the present application, at the time it was filed, was under an obligation of assignment to Sangamo BioSciences, Inc.; which obligation has been fulfilled (*see* Reel 012338, Frame 0701). Thus, according to 35 U.S.C. § 103(c), U.S. Patent 6,607,882 is unavailable as a reference under 35 U.S.C. § 103 against the present application. *See* also MPEP 706.02(l)(1) and MPEP 706.02(l)(2). Accordingly, this rejection is improper and should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: May 25, 2004

By: 
Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicant

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Tel.: (650) 493-3400
Fax: (650) 493-3440